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Can evaluating adrenal glands in computed tomography contribute to predicting the prognosis of hospitalized COVID-19 patients?

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Abstract. – OBJECTIVE: The novel coronavirus disease 2019 (COVID-19) may affect the adrenal glands. Therefore, it is important to evaluate the morphologic appearance of the adrenal glands by thorax computed tomography (CT). On CT scans, stranding in peripheral fatty tissue with enlarged adrenal glands may indicate signs of adrenal infarction (SAI). The present study aimed to evaluate the incidence of SAI and determine whether this finding may contribute to predictions of the prognosis of COVID-19.

PATIENTS AND METHODS: A total of 343 patients who had been hospitalized at Malatya Training and Research Hospital between September 1 and 30, 2020, with a diagnosis of COVID-19 were enrolled in this study. All patients underwent thorax CT scans that included their adrenal glands.

RESULTS: Of the enrolled patients, 16.0% had SAI. Moreover, 41.8% of patients with SAI and 15.3% of patients without SAI were treated in the Intensive Care Unit (ICU). Patients with SAI had a significantly higher rate of ICU admission ($p < 0.001$). Mortality rates were also significantly higher among patients with SAI than those without $p < 0.001$).

CONCLUSIONS: In this study, it was found that COVID-19 patients with SAI may have a poorer prognosis. More comprehensive studies are needed on this subject, but the present study may provide helpful preliminary information in terms of prognosis.

Key Words:
COVID-19, Computed tomography, Adrenal gland.

Abbreviations

(COVID-19): Coronavirus Disease 2019; CT: Computed Tomography; SAI: Signs Of Adrenal Infarction; SARS-Cov-2: Severe Acute Respiratory Syndrome Coronavirus 2; ACE 2: Angiotensin-Converting Enzyme 2; ICU: Intensive Care Unit; HPA: Hypothalamic-Pituitary-Adrenal; BMI: Body Mass Index.

Introduction

The World Health Organization declared the novel coronavirus disease 2019 (COVID-19) caused by severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) to be a pandemic on March 11, 2020[1]. SARS-CoV-2 primarily attacks the lungs, often causing acute respiratory distress syndrome and viral pneumonia complicated by sepsis. The virus enters the host's pneumocytes via the angiotensin-converting enzyme 2 (ACE2) receptor. The ACE2 receptor is expressed in the vascular endothelial cells of many organs, such as the adrenal glands. In autopsy studies of patients who died in the first SARS outbreak in 2003, degeneration and necrosis were detected in the cortical cells of the adrenal glands. SARS-CoV, belonging to the same family as SARS-CoV-2, was identified in the adrenal glands, indicating the direct cytopathic effects of the virus[2]. Pneumonia, sepsis, and respiratory failure are common complications in hospitalized COVID-19 patients. Moreover, some patients develop severe systemic disease and multiple organ dysfunction[3]. SARS-CoV-2 infection can cause coagulation system activation, and coagulation imbalances may occur in association with high levels of pro-inflammatory markers[4]. Recent studies have revealed thrombotic complications in 16-49% of COVID-19 patients admitted to the ICU[5]. The intensive inflammatory process in COVID-19 is usually associated with the activation of coagulation[6]. This phenomenon has also been observed in infections of Neisseria meningitidis, Mycobacterium tuberculosis, Cytomegalo virus, Ebola virus, and Histoplasma capsulatum, often resulting in bleeding and/or thrombosis-related adrenal damage[7].

The adrenal glands play a central role in the response to stress in the hypothalamic-pituitary-adrenal (HPA) axis. Rapid and adequate adrenal hormone release is necessary for survival in cases of severe infection and septic shock[8]. Studies on HPA

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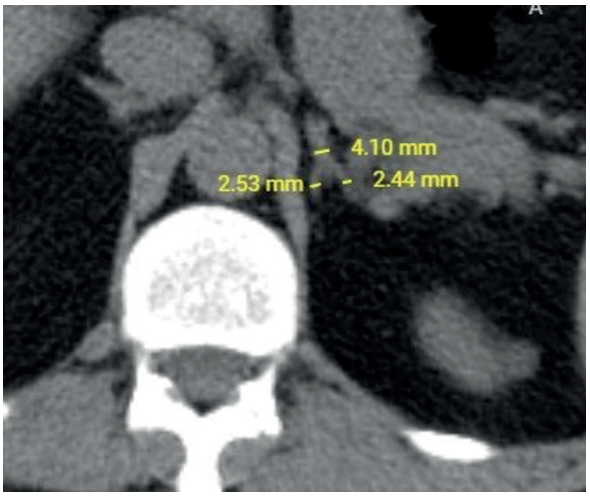

Figure 1. The left adrenal gland of normal size.

axis dysfunction are available in the literature, but there is still uncertainty about the pathophysiology of the immune response affecting the adrenal gland[9].

Most patients hospitalized for COVID-19 undergo non-contrast thoracic computed tomography (CT). In most CT scans, the adrenal glands are included in the visual field. Considering that SARS-CoV-2 may affect the adrenal glands, it is important to evaluate signs of adrenal infarction (SAI) in the adrenal glands on CT scans. SAI presents on CT scans as the presence of stranding in the peripheral fatty tissue with enlarged adrenal glands[10]. The aim of this study is to evaluate the incidence of SAI and determine whether this finding may contribute to predictions of the prognosis of COVID-19.

Patients and Methods

In this retrospective study, non-contrast thoracic CT scans were retrospectively evaluated for all patients who were hospitalized at Malatya Training and Research Hospital between September 1 and 30, 2020, with the diagnosis of COVID-19. Cases of COVID-19 were confirmed by reverse transcription polymerase chain reaction (RT-PCR) positivity for SARS-CoV-2 based on nasopharyngeal swab samples. Of those patients, 343 patients whose adrenal glands were fully included in the CT imaging area were enrolled in the study. The CT scans were performed using a Philips Medical System MX-16-Slice Multidetector (Koninklijke Philips N.V., Eindhoven, the Netherlands). The tube voltage was 110 kV. CT images were transferred to post-processing workstations for multiplanar reconstructions and maximum intensity projection reconstructions. Two radiologists with ten and eight years of respective experience retrospectively evaluated the CT images via the hospital's picture archiving and communication system (PACS). The images were evaluated at the same time by these two radiologists, who were unaware of the clinical findings and prognoses of the patients. In evaluating the sizes of the adrenal glands, measurements greater than 7 mm for the maximum width perpendicular to the long axis of the trunk and 3 mm for the maximum width of the medial and lateral limbs reflected enlargement[10,11]. The measurement method is depicted in Figure 1. Along with enlargement of the adrenal glands, the streaking of fatty tissue in the periphery of a gland was evaluated as SAI in the CT images (Figures 2A-B).

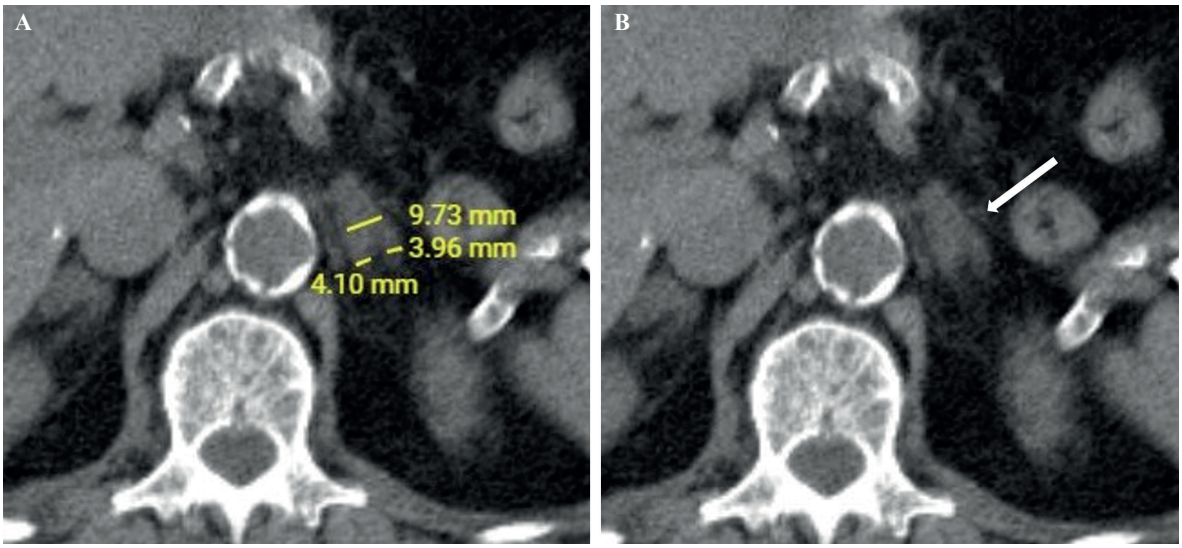

Figure 2. A, The enlarged left adrenal gland. **B**, In the same patient, arrow shows stranding in peripheral fatty tissue.

SAI was accepted as present in all patients with bilateral or unilateral SAI. The lung involvement area was evaluated as described by Pan et al[12]. Subsequently, two groups of patients were established considering the degree of lung parenchymal involvement as <50% involvement and ≥50% involvement. The length of hospital stay, whether the patient was hospitalized in the ICU, recovery status, presence of comorbidities, and height and weight were obtained from the hospital's information system. Comorbid disease status was evaluated according to the CDC classification. Body Mass Index (BMI) was calculated as body weight (kg) divided by height squared (m^2).

In biochemical analysis, the blood glucose, sodium, and potassium values measured on the day of the patients' CT scans were recorded and grouped according to hospital reference values.

Statistical Analysis

IBM SPSS Statistics for Windows 22.0 (IBM Corp., Armonk, NY, USA) was used to analyze the data. Chi-square, *t*-test, and logistic regression analyses were performed for statistical evaluation. Logistic regression analysis was applied to determine the variables that might affect mortality. Odds ratios were calculated with 95% confidence intervals. Values of $p < 0.05$ were considered statistically significant.

Ethics Approval

This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Malatya Clinical Ethics Committee (approval No: 2021/22).

Results

Of the 343 patients included in this study, 196 (57.1%) were male. Patients were between 21 and 96 years old, with a mean age of 66.50 ± 13.94 years. While 206 (60.1%) of the patients had at least one comorbid disease, 46 (13.4%) of the patients had bilateral SAI and 9 (2.6%) patients had unilateral SAI. Pulmonary parenchymal involvement was ≥50% in 75 (21.9%) of these cases. Additionally, 67 of the patients (19.5%) were treated in the ICU. These findings are outlined in Table I.

While the percentage of SAI was not statistically different between the genders ($p = 0.308$), the mean age of patients with SAI was statistically higher than the mean age of those without ($p < 0.001$). Of the patients with SAI, 41.8% were admitted to the ICU, while among patients without SAI, only 15.3% were admitted to the ICU. The rate of ICU admission was significantly higher among patients with SAI ($p < 0.001$). Mortality rates were also higher among those with SAI than those without; 45.5% of patients with SAI and 17.0% of patients without SAI died ($p < 0.001$). Pulmonary parenchymal involvement of 50% or more was considered as severe disease. Lung involvement was above 50% in 36.4% of the patients with SAI and in 19.1% of the patients without SAI, and this difference was significant ($p = 0.005$). These findings are given in Table I. None of the patients had hypoglycemia. However, 27.3% of the patients with SAI and 15.3% of the patients without SAI had hyperkalemia, and this difference was significant ($p = 0.031$). Additionally, 14.5% of the patients with SAI and 11.1% of the patients with-

Table I. Comparison of demographic, clinical and CT characteristics of patients among patients with and without SAI.

Characteristics	SAI present [n (%) or] mean±SD	SAI is absent [n (%) or] mean±SD	All n (%) or mean±SD	*p*-value
Mean age±SD	73.56±12.87	65.15±13.74	66.50±13.94	<0.001
Mean BMI±SD	27.62±4.63	28.06±4.42	27.99±4.45	0.504
Male	28 (50.9)	168 (58.3)	196 (57.1)	0.308
Female	27 (49.1)	120 (41.7)	147 (42.9)	
Lung I <%50	35 (63.6)	233 (80.9)	268 (78.1)	0.005
Lung I ≥%50	20 (36.4)	55 (19.1)	75 (21.9)	
Comorb+	36 (65.5)	170 (59.0)	206 (60.1)	0.373
Comorb-	19 (34.5)	118 (41.0)	137 (39.9)	
ICU	23 (41.8)	44 (15.3)	67 (19.5)	<0.001
Non-ICU	32 (58.2)	244 (84.7)	276 (80.5)	
Death	25 (45.5)	49 (17.0)	74 (21.6)	<0.001
Discharged	30 (54.5)	239 (83.0)	269 (78.4)	

n = number of patients; SD: Standard deviation; Lung I: Lung involment; Comorb+: Patients with at least one comorbid disease; Comorb: no comorbid disease.
p-value for age and BMI was calculated using the *t*-test, and the *p*-value for the others was calculated using the chi square test.

out SAI had hyponatremia; this difference was not significant ($p = 0.467$).

A total of 75 patients showed lung involvement equal to or greater than 50%, considered as cases of severe lung involvement. These patients were assessed separately. No relationship was identified between age and gender in the presence of SAI among patients with severe lung involvement ($p = 0.105$ and 0.284, respectively). In patients with severe lung involvement, the rate of hospitalization and the mortality rate in the ICU in the presence of SAI were statistically higher compared to cases without SAI ($p = 0.018$ and $p = 0.021$, respectively). Figure 3 summarizes the prognosis status of patients according to lung involvement percentages and presence of SAI.

Logistic regression analysis was used to assess the relationships of independent variables such as age, gender, SAI, comorbid diseases, and BMI with mortality as the indicator of poor prognosis. It was determined that age, gender, SAI, lung involvement, and BMI had significant relationships with mortality ($p < 0.05$). The results of this analysis are given in Table II.

Discussion

ACE2 receptors are entry points for SARS-CoV-2. Therefore, the widespread presence of ACE2 receptors in the body constitutes a risk factor for multiple organ involvement, including the endocrine system[13,14]. Since endocrine and immunological responses are closely related, both systems are expected to affect each other in cases of COVID-19[15,16]. Three main interaction mechanisms between SARS-CoV-2 and the endocrine system are currently hypothesized. These are direct infection of the glands with the virus, activation of the HPA axis with cytokines, and the formation of antibodies or glandular damage secondary to cellular damage[17].

The incidence of thrombotic complications is also known to increase in COVID-19 patients. It is assumed that increased cytokine levels in COVID-19 may cause coagulation or give rise to an increased prothrombotic profile with direct damage to endothelial cells[18]. Catecholamines released in the procoagulant setting in critical patients may cause vasoconstriction in the adrenal veins, causing venous thrombosis and adrenal necrosis. Previous studies have proposed that adrenal vein thrombosis due to hypercoagulation leads to adrenal infarction[19]. This condition may be complicated by necrosis of the adrenal gland, reperfusion injury, or bleeding after anticoagulant use[20].

In severe cases of COVID-19, the frequency of SAI may be increased due to increased thrombotic complications. In the current study, the incidence of SAI was 26.7% in patients with severe lung involvement, while it was 13.1% in patients with lung

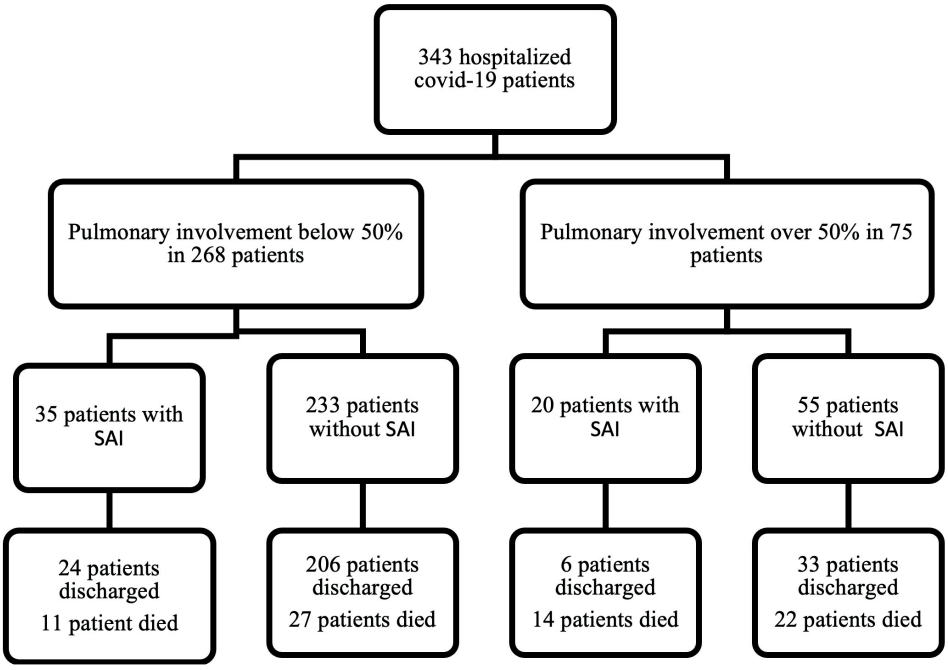

Figure 3. Prognosis status of patients according to lung involvement percentages and presence of SAI.

Table II. Logistic regression analysis for probable independent associated factors with mortality as dependent prognostic factor.

Independent Variables	Beta	Wald	Standard error	p-value	Odds ratio Exp(B)	Odds ratio 95% CI	
						Lower	Upper
Age	.062	16.723	.015	.000	1.064	1.033	1.095
Gender	.722	4.967	.332	.026	2.058	1.091	3.881
SAI	1.087	9.244	.358	.002	2.966	1.472	5.979
Lung I <50% ≥50%	1.521	22.769	.319	.000	4.577	2.451	8.550
Comorbid	.488	2.183	.330	.140	1.628	.853	3.109
BMI	.127	11.912	.037	.001	1.135	1.056	1.220
Constant	-10.58	32.171	1.867	.000	.000		

CI: Confidence Interval; Lung I: Lung involvement.

involvement below 50% ($p = 0.005$). This may indicate increased frequency of SAI in patients with severe lung involvement. It may also indicate the worsening of prognosis in the presence of infarction.

An autopsy study of 28 patients who died of severe COVID-19 showed adrenal lesions in 12 (42.9%) cases. Adrenal necrosis was observed in 7 of the 12 cases of adrenal lesions[21]. In another autopsy study of 5 patients, acute fibrinoid necrosis was observed in the small vessels of the adrenal parenchyma, and especially the arterioles, on microscopic examination. In this study, vascular pathology was more prominent in the adrenal glands than in other organs[22].

In the current study, the rate of ICU admission and the rate of mortality among patients with SAI were significantly higher compared to those without SAI. In a study on the effects on prognosis of SAI findings on CT scans of COVID-19 patients with severe lung involvement, the ICU admission rate was higher among patients with SAI than patients without SAI. Furthermore, acute adrenal infarction was reported to be frequent in the first lung evaluations of patients with severe COVID-19, indicating the possibility of a worse prognosis[23]. Similar to the current study, the ICU admission rate was higher in patients with SAI[23]. In the present work, as a result of our logistic regression analysis, it was determined that SAI had a significant effect on mortality and therefore prognosis in cases of COVID-19 ($p < 0.001$).

In the case of adrenal insufficiency, clinical signs and symptoms are generally not specific to the disease and often lead to delays in diagnosis or even misdiagnosis[24]. After the initial clinical evaluation, sodium, potassium, cortisol, and adrenocorticotropic hormone (ACTH) levels should be evaluated, and abdominal imaging should be used for diagnosis when appropriate[18]. In the current study, blood glucose, sodium, and potassium values were available for all patients, but none of the patients had undergone the cortisol tests or ACTH stimulation tests that are required to diagnose adrenal insufficiency. None of the patients had hypoglycemia, but 27.3% of the patients with SAI and 15.3% of the patients without SAI had hyperkalemia and that difference was statistically significant ($p = 0.031$). Furthermore, 14.5% of the patients with SAI and 11.1% of the patients without SAI had hyponatremia, but that difference was not statistically significant ($p = 0.467$). In an autopsy study of COVID-19 patients, plasma samples collected and stored for 1 or 2 days before death from patients with adrenal lesions in the autopsy findings were sent for cortisol measurements. As a result, no patients had cortisol values of <10 µg/dL, which is a reliable and common laboratory marker of adrenal insufficiency in critical cases[21]. However, another study suggested that steroid usage would be beneficial in COVID-19 patients with critical illness[25]. In other words, the relationship between COVID-19 and the adrenal glands is still open to discussion.

Conclusions

The presence of SAI in CT is not specific to COVID-19. It is also an occasionally incidental and negligible finding in the tomography images taken for other diseases. In this study, we found that COVID-19 patients for whom SAI was detected on CT scans may have a worse prognosis. There is still a need for more comprehensive research on this subject. However, based on initial findings, it seems that identification of SAI on CT scans may provide preliminary information in terms of prognosis.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Authors' Contribution

Conceptualitazion: Mehtap Ilgar, Serkan Ünlü, Mehmet Akçiçek. Data curation: Mehtap Ilgar, Serkan Ünlü, Mehmet Akçiçek. Formal analysis: Mehtap Ilgar, Serkan Ünlü. Investigation: Mehtap Ilgar, Serkan Ünlü, Mehmet Akçiçek. Project administration: Mehtap Ilgar. Visualization: Mehtap Ilgar, Serkan Ünlü. Writing – orginal draft: Mehtap Ilgar, Serkan Ünlü, Mehmet Akçiçek. Writing-review and editing: Mehtap Ilgar, Serkan Ünlü, Mehmet Akçiçek.

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Ethical Approval

This retrospective study recieved approval from Malatya Clinic Ethics Committee. Protocol number is 2021/22.

Informed Consent

Informed consent was not required due to the retrospective nature of the study.

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